DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 2 0 2000

99-HFD-46-0901

# WARNING LETTER

**Certified Mail-Restricted Delivery**
**Return Receipt Requested**

Mr. Robert Z. Martin
Vice President of Operations
Heyltex Corporation
10655 Richmond Avenue
Houston, TX 77042

Dear Mr. Martin:

On October 27, October 28, and November 10, 1998, Ms. Andrea A. Branche, representing the Food and Drug Administration (FDA), inspected Heyltex Corporation's conduct as the sponsor of two investigational new drugs (INDs) -[ ] (IND #[ ] and [ ] IND [ ] At the conclusion of the inspection, Ms. Branche issued you a Form FDA 483 and discussed with you the inspectional observations.

From our review of your IND applications, and our evaluation of the inspection report, the documents collected during the inspection, and your responses to the inspectional observations, **we conclude that you failed to meet the responsibilities of a sponsor as specified in Federal regulations, as follows:**

1. **a. Failure to notify FDA of serious unexpected adverse experiences associated with the use of the study drug [Title 21, Code of Federal Regulations, part 312.32(c) (21 CFR 312.32(c))]**

   You failed to notify FDA by telephone, within three working days of your initial receipt, of information about an unexpected fatality associated with the use of a study drug, and failed to notify FDA and all participating investigators by a written safety report within ten working days after your initial receipt of the information.

Given the information provided in source documents and the protocol, we conclude that this death meets the regulatory standard for reporting of serious and unexpected adverse events associated with the use of the study drug. No records were available, however, during the inspection of your firm or in FDA files, to document that you notified FDA by telephone of the death of subject[ ]who died in 1997 while in the [ ]study. Nor were any records available during the inspection or in FDA files to document that you provided a written safety report to FDA.

In explanation, you stated that Heyltex had never actually started the proposed Phase 3 study, but that the[ ]site (also known as[ ] was simply conducting a "test" of the proposed study protocol. However, 21 CFR 312.3 defines a "clinical investigation" as "***any experiment*** in which a drug is administered or dispensed to, or used involving one or more human subjects. For purposes of this part, an experiment is ***any use of a drug except for the use of a marketed drug in the course of medical practice***." [Emphasis added.] The administration of [ ]to 16 study subjects by[ ]did indeed constitute a clinical investigation within the meaning of 312.3, subject to the requirements outlined in 21 CFR 312 for the conduct of such studies.

**b. Failure to review safety information as it is obtained [21 CFR 312.32(b) and 312.56(c)]**

You failed to review and evaluate the evidence relating to the safety and effectiveness of the drug as the evidence was obtained. No records were available during the inspection to document that you reviewed and evaluated the cause of Subject DM's death.

**c. Failure to list subjects who died during participation in the study and the cause of death in the annual report submitted to the IND [21 CFR 312.33(b)(3)]**

The Annual Report that you submitted to your IND [ ]on January 12, 1998, states "During the last year, no safety reports related to the use of[ ]were submitted to the Agency", and "No subjects have died during participation in any investigation during the past year." The monitor learned of Subject [ ]death on September 22, 1997, and informed you about the death on September 24, 1997.

**2. Failure to select investigators qualified by training and experience to study the drug [21 CFR 312.53(a)]**

The "Statement of Investigator" (Form FDA 1572) lists[ ]Ph.D., as the investigator; no sub-investigators are listed for the[ ]site. Dr. [ ]curriculum vitae fails to demonstrate that she is qualified by experience and training as an appropriate expert to investigate this investigational drug.

3. **Failure to notify FDA when an investigator's participation in a study is terminated due to noncompliance [21 CFR 312.56(b)]**

   In your letter of September 26, 1997, you terminated the participation of [ ]Ph.D., as an investigator for the phase III clinical study "A Protocol for Studying Mobilization of Mercury by Giving [ ]Intravenously and Intramuscularly to Humans." No records were available during the inspection to document that you reported this termination to FDA as required by Federal regulations.

4. **Failure to ensure proper monitoring of the investigation [21 CFR 312.50]**

   No record was available for any study monitoring prior to Ms. [ ] monitoring report of March 1998, for a study conducted by [ ] Ph.D., entitled [ ]-Mercury Challenge Test, Intravenous" [ ]Dental Study), under IND [ ]The study took place at the [ ] from 3/12-14/98.

   The Forms FDA 1571, dated July 5, 1994, February 17, 1997, June 27, 1997, and June 6, 1999, list you ("Robert Z. Martin, Vice President, Operations, Heyltex") as the monitor. You stated during the inspection, however, that you never monitored any study, and no records were available during the inspection to document that you indeed did any monitoring.

   The Form FDA-1571, dated August 22, 1996, lists Dr. [ ]the principal investigator for the study, as the monitor. No record was available during the inspection to document any monitoring by Dr. [ ]

5. **Failure to ensure that an Institutional Review Board (IRB) would be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigations [21 CFR 312.23(a)(1)(iv)]**

   No records were available during the inspection to document IRB review and approval of the [ ]Dental Study". No records were available during the inspection to document IRB review and approval of four protocol amendments to the study conducted by the [ ]

**6. Failure to provide a summary of the status of each study [21 CFR 312.33(a)]**

You submitted an annual report on January 12, 1998, which states "No study has been performed during the period August 1, 1996, to December 31, 1997." During that period you shipped 50 ampoules of the investigational drug to the [ ]The Drug Accountability Log for the [ ]identifies sixteen subjects who received the study drug between July 22, 1997, and September 19, 1997. Subject[ ]was given two doses of the study drug in 1997 and died in September 1997.

**7. Failure to submit annual reports within 60 days of the anniversary dates that the INDs went into effect [21 CFR 312.33]**

a) You submitted a total of six annual reports to FDA for two INDs, from 1994-1999. Nine reports should have been submitted during this time period for these two INDs.

b) Only one of the six annual reports that you filed was within sixty days of an anniversary date. [See chart below.]

| Annual Report Filing Dates – Heyltex | | | |
|---|---|---|---|
| IND# | Effective Date of IND | Date Annual Report due (within 60 days of anniversary date) | Date Report Filed |
| [ ] | 4/2/95 | 4/2/96 – 6/2/96 | 8/22/96 |
| | | 4/2/97 – 6/2/97 | 1/12/98 |
| | | 4/2/98 – 6/2/98 | 1/6/99 |
| | | 4/2/99 – 6/2/99 | Not Filed |
| | | | |
| [ ] | 8/5/94 | 8/5/95 – 10/5/95 | 9/11/95 |
| | | 8/5/96 – 10/5/96 | 2/17/97 |
| | | 8/5/97 – 10/5/97 | Not Filed |
| | | 8/5/98 – 10/5/98 | 10/20/98 |
| | | 8/5/99 – 10/5/99 | Not Filed |

**8. Failure to maintain adequate records that include the name of the investigator to whom the study drug was shipped [21 CFR 312.57(a)]**

The records of the '[ ]Tracking System" show the sites where the drug was sent, but fail to name the investigator to whom the drug was shipped.

In conclusion, as summarized above, FDA's inspection documented that you failed to meet the responsibilities of a sponsor as specified by Federal regulations. Within 15 calendar days of your receipt of this letter, provide this office with your written response to the following:

1. Your written explanation of why each of the problems identified above occurred.

2. Your written description of the specific corrective actions you have taken and are taking to ensure that problems, similar to those described above, will not recur and to ensure the validity, accuracy and reliability of your current and future data.

3. A copy of your revised monitoring SOPs that will ensure proper monitoring of clinical studies in the future.

You should send your written response to my office at the address shown.

The above discussion of violations is not intended to be a complete list of the deficiencies at Heyltex Corporation. Your failure to promptly correct these deficiencies may result in regulatory action without further notice.

We appreciate the cooperation shown Ms. Branche during the inspection.

Sincerely yours,

Stan W. Woollen
Acting Director
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Office of Medical Policy
Center for Drug Evaluation and Research
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